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Topical Ivermectin: Data Supporting Dual Modes of Action in Rosacea

ABSTRACT

Until recently, the potential modes of action of topical ivermectin in rosacea have been speculated but not studied. Short-term studies (12 week), long-term studies (up to 52 weeks), and case report series have now been completed, and topical ivermectin (IVM), formulated as a 1% cream that is applied once daily, has been shown to be effective, well-tolerated, and safe for the treatment of rosacea. This article reviews outcomes from studies that support dual modes of action, including both anti-inflammatory and anti-parasitic effects.

KEYWORDS: Ivermectin, topical formulation, rosacea

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MANAGEMENT OF PAPULOPUSTULAR rosacea (PPR) has improved substantially over the past several years with the development of therapies approved by the United States Food and Drug Administration (FDA), such as azelaic acid (AzA) 15% gel and foam, sub-antibiotic dose doxycycline (SDD), and topical ivermectin (IVM) 1% cream.[1] The latter is the most recent addition to the armamentarium, with multiple studies demonstrating efficacy in PPR, with favorable skin tolerability and no concerning safety signals.

In two 12-week, pivotal, Phase III trials of adults with papulopustular rosacea, IVM 1% cream applied once daily proved to be superior to vehicle based on both investigator global assessment (IGA) success rates and inflammatory lesion reductions, and was shown to be safe and well tolerated.[2] Further evaluations included two 40-week extension studies from these pivotal trials to determine the long-term safety of IVM 1% cream using azelaic acid (AzA) 15% gel as an active comparator; the latter was started only after initiation of the 40-week extension phase.[3] Subjects originally treated in the pivotal trials with IVM 1% once daily were continued on this same therapy, and those subjects treated originally with vehicle cream once daily were switched to AzA 15% gel twice daily. Both IVM 1% cream and AzA 15% gel were safe and well tolerated overall throughout the study, with a lower incidence of related adverse events (AEs) in the IVM 1% cream group compared to AzA 15% gel group. Additionally, IVM 1% cream demonstrated continued efficacy during the 40-week extension studies, with a higher percentage of

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subjects exhibiting IGA endpoint success (rated as clear or almost clear) at the end of the study compared to baseline.[3] A more recent network meta-analysis (57 studies identified; 19 providing data suitable for mixed treatment comparisons) suggests that IVM 1% cream is a more effective topical treatment for PPR with regard to lesion reduction than other currently available options, with at least an equivalent safety and tolerability profile.[4] The results of a 36-week extension study in subjects with moderate-to-severe PPR who were successfully treated during the initial 16-week randomized study phase with either IVM 1% cream once daily or metronidazole 0.75% cream twice daily showed that IVM 1% was more efficacious and markedly extended remission of PPR after cessation of therapy as compared to initial treatment with metronidazole 0.75% cream.[5] Additional publications have documented several case reports of papulopustular rosacea effectively treated with IVM 1% cream, with real world experience being consistent with results from clinical studies.[6,7]

Although more data are needed on the modes of action (MOA) of currently available therapies for PPR, there are data that suggest certain MOA for both azelaic acid and tetracyclines that appear to correlate with pathophysiologic pathways believed to be operative in rosacea.[8-11] Despite the multiple studies and high-quality level of evidence supporting the use of IVM 1% cream for treatment of PPR, there has been limited research on MOA of topically applied IVM specifically for rosacea.[12] This article reviews new information from studies that evaluate potential MOA of IVM 1% cream in rosacea.

IMPACT OF IVERMECTIN ON INNATE IMMUNE DYSREGULATION IN ROSACEA

Two major pathophysiologic mechanisms reported to be involved in the pathogenesis of rosacea are neurovascular dysregulation and augmented innate and adaptive immune response.[13-18] Upregulation with increased epidermal levels of cathelicidin antimicrobial peptides (AMPs) has been demonstrated in rosacea-affected skin; excessive production of both cathelicidin (LL-37) and kallikrein-5 (KLK5), the predominant serine protease enzyme responsible for cleavage of LL-37 from an inactive precursor form, has been suggested to play a pathophysiologic role in rosacea.[18,19] Research studies with IVM were completed using either normal human epidermal keratinocytes (NHEK), reconstructed human epidermis (RHE) or human skin *ex-vivo* stimulated with calcitriol (1α,25-dihydroxyvitamin D3), which is known to upregulate the expression of KLK5 and LL-37.

The study showed that IVM can inhibit KLK5 gene expression in the epidermis, which would result in reduction in the inflammation in rosacea that is triggered by augmented abnormal LL-37 processing.[20] IVM was shown to inhibit KLK5, cathelicidin gene expression, and protein secretion in NHEK cells stimulated with calcitriol, with these outcomes also verified in the experiments using three dimensional (3D) skin models (RHE and skin *ex vivo*). Importantly, the anti-inflammatory properties of IVM were associated with inhibition of IL-8, IL-6, and monocyte chemoattractant protein 1 (MCP-1; chemokine ligand 2 [CCL2]) secretion from NHEK cells, thus supporting that IVM may provide direct biologic effects that are anti-inflammatory in rosacea and are unrelated to its anti-parasitic properties.[20]

IMPACT OF IVERMECTIN ON DEMODEX MITES IN ROSACEA

Although the role of Demodex mites in the pathophysiology of rosacea has remained controversial for over eight decades, there is good evidence that a proliferation of these mites in facial skin can contribute to the emergence of clinical manifestations of rosacea.[21-25] Refinements in methodology and tools to assess the presence and quantification of Demodex mites has assisted researchers in evaluating their role in rosacea.[25] In the preclinical and pivotal clinical studies completed with IVM 1% cream during the formal development program, antiparasitic activity against Demodex mites was not examined. In order to assess whether IVM 1% cream has activity against Demodex mites in individuals with rosacea, a pilot study was performed in Caucasian subjects (N=20) with moderate-to-severe rosacea.[26] For inclusion in the study, the protocol mandated an IGA score or 3 or greater and a Demodex mite density of 15/cm^2 or more. All subjects applied IVM 1% cream once daily for at least 12 weeks. Demodex mite density was evaluated by skin surface biopsies. Inflammatory and immune biomarker expressions were determined with real time polymerase chain reaction (RT-PCR) and with use of immunofluorescence staining.[26]

The study outcomes showed that IVM 1% cream markedly reduced Demodex mite density and reduced gene expression of several biomarkers, which may explain, at least partially, its MOA in rosacea. Mean density of Demodex mites was significantly decreased at both Week 6 and Week 12 ($p<0.001$). In addition, the gene expression levels of IL-8, LL-37, human β-defensin-3 (HBD3), Toll-like receptor-4 (TLR4), and tumor necrotic factor-alpha (TNF-α) were downregulated at week 6 and week 12. The gene expression reductions were statistically significant for LL-37, HBD3 and tumor necrosis factor-alpha (TNF-α) at both follow-up time points ($p<0.05$) and at Week 12 for TLR4 ($p<0.05$). Importantly, reduced expression of LL-37 ($p<0.05$) and IL-8 were confirmed based on their protein levels determined by immunofluorescence staining. Clinical outcomes were also captured, with all subjects demonstrating visible improvement and 80 percent of subjects (16/20) achieving a clear or almost clear IGA rating (IGA score ≤1).[26]

TABLE 1. Potential dual modes of action of topical IVM in rosacea

Anti-inflammatory effects via suppression of augmented innate immune response
Benchtop experiments were completed using either NHEK, RHE, or human skin *ex-vivo* stimulated with calcitriol (1α,25-dihydroxyvitamin D3) to upregulate the expression of KLK5 and LL-37.
IVM inhibited KLK5 and CAMP gene expression and protein secretion in NHEK cells stimulated with calcitriol, and in the experiments using 3D skin models (RHE and skin *ex vivo*).
IVM reduced secretion of IL-8, IL-6 and MCP-1 (CCL2) from NHEK cells.
A pilot study was completed in subjects with rosacea to evaluate the effects of IVM 1% cream applied once daily on Demodex mites and its impact on the expression of multiple biomarkers associated with cutaneous inflammation in these same subjects (N=20).
Mean density of Demodex mites was significantly decreased by IVM 1% cream at Week 6 and Week 12 ($p<0.001$).
Gene expression levels of IL-8, LL-37, HBD3, TLR4, and TNF-α were decreased at Week 6 and Week 12. Gene expression reductions were statistically significant for LL-37, HBD3, and TNF-α at both Week 6 and Week 12 ($p<0.05$), and at Week 12 for TLR4 ($p<0.05$).
Reduced expression of LL-37 ($p<0.05$) and IL-8 were confirmed based on their protein levels determined by immunofluorescence staining.
All subjects demonstrated clinical improvement in rosacea over the duration of the study, determined by immunofluorescence staining. Eighty percent of subjects (16/20) achieved a clear or almost clear IGA rating (IGA score ≤1)

IVM: ivermectin; NHEK: normal human epidermal keratinocytes; RHE: reconstructed human epidermis; KLK5: kallikrein-5; LL-37: cathelicidin; CAMP: cathelicidin antimicrobial peptide; 3D: three dimensional; IL: interleukin; MCP-1: monocyte chemoattractant protein 1; CCL2: chemokine ligand 2; HBD3: human β-defensin-3;TLR4: Toll-like receptor-4; TNF: tumor necrotic factor; IGA: investigator global assessment

SUMMARY

Several publications support the efficacy and safety of IVM 1% cream applied once daily for treatment of rosacea, based on pivotal Phase III studies, long-term extension studies, and additional case report series. Basic science experiments using human epidermal keratinocytes, reconstructed human epidermis, and human skin *ex vivo*, and a pilot study in patients with rosacea show that IVM 1% cream appears to modulate the pathophysiology of rosacea through at least the following MOA: 1) inhibition of the cathelicidin pathway, which is augmented in rosacea-affected skin, and 2) reduction in the density of Demodex mites along with decreased expression of multiple biomarkers related to cutaneous inflammation in rosacea (Table 1). Hopefully, additional studies will be completed to further elucidate MOA of IVM 1% cream in rosacea and possibly other inflammatory dermatoses affecting facial skin.

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